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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07K 5/023, A61K 38/06, C07D 471/04, 498/04, A61K 31/495 // (C07D 471/04, 233:00, 221:00) (C07D 498/04, 263:00, 241:00)

A1

(11) International Publication Number: **WO 98/58947**

(43) International Publication Date: 30 December 1998 (30.12.98)

(21) International Application Number: PCT/IB98/00873

(22) International Filing Date: 5 June 1998 (05.06.98)

(30) Priority Data:
60/050,764 25 June 1997 (25.06.97) US

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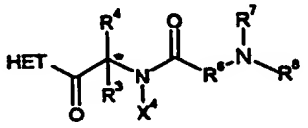
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: DIPEPTIDE DERIVATIVES AS GROWTH HORMONE SECRETAGOGUES



(I)

102 & 103

(57) Abstract

This invention is directed to compounds of formula (I), and the pharmaceutically-acceptable salts thereof, where the substituents are as defined in the Specification, which are growth hormone secretogogues and which increase the level of endogenous growth hormone. The compounds of this invention are useful for the treatment and prevention of osteoporosis and/or frailty, congestive heart failure, frailty associated with aging, obesity; accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or patients having undergone major surgery; improving muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis or renal homeostasis. The compounds of the present invention are also useful in treating osteoporosis and/or frailty when used in combination with: a bisphosphonate compound such as alendronate; estrogen, premarin, and optionally progesterone; an estrogen agonist or antagonist; or calcitonin, and pharmaceutical compositions useful therefor. Further, the present invention is directed to pharmaceutical compositions useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprises an effective amount of a compound of the present invention and a growth hormone secretagogue selected from GHRP-6, Hexarelin, GHRP-1, growth hormone releasing factor (GRF), IGF-1, IGF-2 or B-HT920. The invention is also directed to intermediates useful in the preparation of compounds of Formula (I).

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DIPEPTIDE DERIVATES AS GROWTH HORMONE SECRETAGOGUES

This invention relates to dipeptide compounds which are growth hormone secretagogues and are useful for the treatment and prevention of osteoporosis and/or frailty.

Background of the Invention

Growth hormone (GH), which is secreted from the pituitary gland, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body:

1. Increased rate of protein synthesis in substantially all cells of the body;
2. Decreased rate of carbohydrate utilization in cells of the body; and
3. Increased mobilization of free fatty acids and use of fatty acids for energy.

Deficiency in growth hormone results in a variety of medical disorders. In children, it causes dwarfism. In adults, the consequences of acquired GH deficiency include profound reduction in lean body mass and concomitant increase in total body fat, particularly in the truncal region. Decreased skeletal and cardiac muscle mass and muscle strength lead to a significant reduction in exercise capacity. Bone density is also reduced. Administration of exogenous growth hormone has been shown to reverse many of the metabolic changes. Additional benefits of therapy have included reduction in LDL cholesterol and improved psychological well-being.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering an agent which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in an expensive product, and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone (e.g., Jacob-Creutzfeld disease). Recently, recombinant growth hormone has become available which, while no longer carrying any risk f disease transmission, is still a very expensive product which must b given by injection or nasal spray.

Most GH deficiencies are caused by defects in GH release, not primary defects in pituitary synthesis of GH. Therefore, an alternative strategy for normalizing serum GH levels is by stimulating its release from somatotrophs. Increasing GH secretion can be achieved by stimulating or inhibiting various neurotransmitter systems in the brain and hypothalamus. As a result, the development of synthetic growth hormone-releasing agents to stimulate pituitary GH secretion are being pursued, and may have several advantages over expensive and inconvenient GH replacement therapy. By acting along physiologic regulatory pathways, the most desirable agents would stimulate pulsatile GH secretion, and excessive levels of GH that have been associated with the undesirable side effects of exogenous GH administration would be avoided by virtue of intact negative feedback loops.

Physiologic and pharmacologic stimulators of GH secretion, which include arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GHRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

Obesity is a major risk factor for diabetes, and a large fraction of NIDDM patients are obese. Both conditions are characterized by elevated circulating insulin levels and suppressed GH levels. GH treatment of GH-deficient adults (Jorgensen, J.O.L., et al., Lancet 1:1221 (1989)), obese women (Richelsen, B., et al., Am J Physiol, 266:E211 (1994)) and elderly men (Rudman, D., et al, Horm Res 36 (Suppl 1):73 (1991)) has been shown to produce increases in lean body, hepatic and muscle mass while decreasing fat mass. Thus, GH therapy for obesity would seem attractive except for the diabetogenic effects of GH.

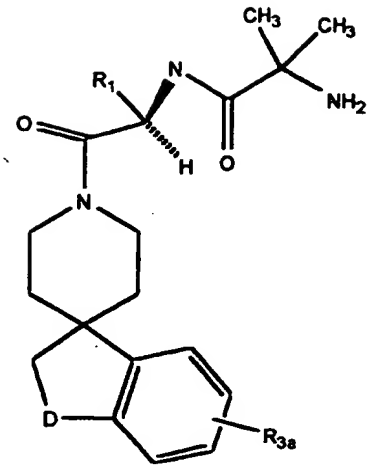
An alternative to exogenous GH administration is therapy that stimulates endogenous GH secretion. It has been shown that a substantial pituitary reserve of GH is present in pituitary-intact GH-deficient patients and the elderly so that decreased serum GH levels are due to hyposecretion.

Hyposecretion of GH in several clinical s ttings (obesity, aging, glucocorticoid suppression) is relatively resistant to stimulation by GHRH (Gertz, B.J., et al., J Clin Endocrinol Metab, 79:745 (1994); Arvat, E., et al., J Clin Endocrinol Metab, 79:1440 (1994); Maccario, M., et al., Metabolism, 44:134 (1995)). In contrast, administration of a GHRP or combined administration of GHRH and a GHRP in these patients can elicit a robust GH response (Aloi, J.A., et al., J Clin Endocrinol Metab, 79:943; (1994)). Single dose studies of GHRPs have demonstrated the absence of an acute effect on circulating insulin or glucose levels. Insulin and glucose have generally not been monitored in chronic studies except to document the absence of unfavorable changes (Jacks, T., et al., J Endocrinol. 143:399 (1993)).

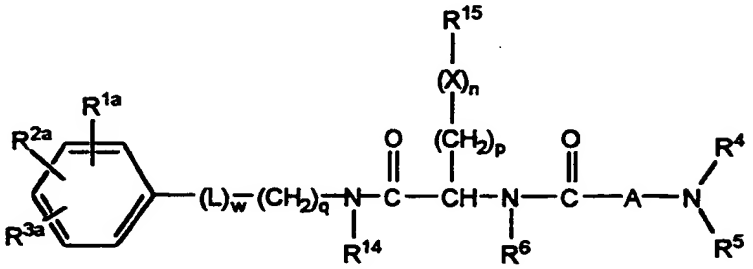
Prior to the present invention, the use of GHRPs or GHRP mimetics to improve glycemic control has not specifically been explored. The method of treating insulin resistance in a mammal comprising the administration of a compound of Formula I of this invention is practiced preferentially in patients who have a functional hypothalamic-pituitary axis capable of GH secretory responses to GHRPs and who have pancreatic beta-cells capable of secreting insulin.

Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent No. 4,411,890. These peptides, while considerably smaller than growth hormones, are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low.

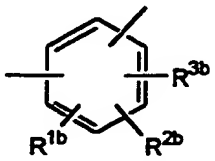
WO 94/13696 refers to certain spiropiperidines and homologues which promote release of growth hormone. Preferred compounds described therein are of the general structure shown below.



WO 94/11012 refers to certain dipeptides that promote release of growth hormone. These dipeptides have the general structure



where L is

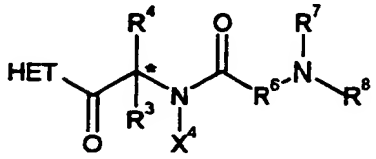


The compounds of WO 94/11012 and WO 94/13696 are reported to be useful in the treatment of osteoporosis in combination with parathyroid hormone or a bisphosphonate.

PCT publication WO 97/09060 discloses the use of growth hormone releasing hormone or a functional analog thereof in the treatment of insulin resistance in mammals.

Summary f th Inventi n

This invention provides compounds of the formula:



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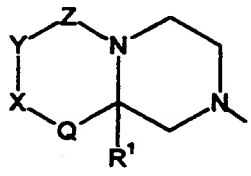
or a stereoisomeric mixture thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomer thereof, or a prodrug of such compound, mixture or isomer thereof, or a pharmaceutically acceptable salt of the compound, mixture, isomer or prodrug,

wherein

HET is a heterocyclic moiety selected from the group consisting of



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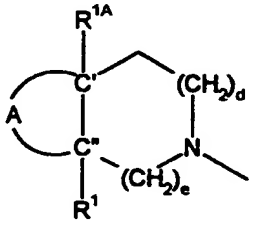

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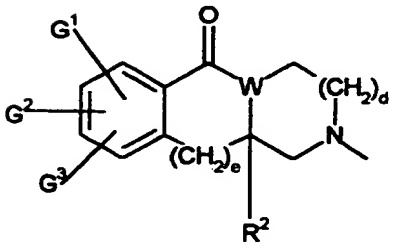
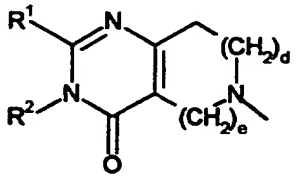


and



d is 0, 1 or 2;

e is 1 or 2;

A is a divalent radical, where the left hand side of the radical as shown below is connected to C" and the right hand side of the radical as shown below is connected to C', selected from the group consisting of

$-NR^2-C(O)-NR^2-$,

$-NR^2-S(O)_2-NR^2-$,

$-O-C(O)-NR^2-$,

-NR^2-C(O)-O-,
-C(O)-NR^2-C(O)-,
-C(O)-NR^2-C(R^9R^{10})-,
-C(R^9R^{10})-NR^2-C(O)-,
-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-,
-$S(O)_z$-C(R^9R^{10})-C(R^9R^{10})-,
-C(R^9R^{10})-O-C(O)-,
-C(R^9R^{10})-O-C(R^9R^{10})-,
-NR^2-C(O)-C(R^9R^{10})-,
-O-C(O)-C(R^9R^{10})-,
-C(R^9R^{10})-C(O)-NR^2-,
-C(O)-NR^2-C(O)-,
-C(R^9R^{10})-C(O)-O-,
-C(O)-NR^2-C(R^9R^{10})-C(R^9R^{10})-,
-C(O)-O-C(R^9R^{10})-,
-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-,
-$S(O)_z$-NR^2-C(R^9R^{10})-C(R^9R^{10})-,
-C(R^9R^{10})-C(R^9R^{10})-NR^2-C(O)-,
-C(R^9R^{10})-C(R^9R^{10})-O-C(O)-,
-NR^2-C(O)-C(R^9R^{10})-C(R^9R^{10})-,
-NR^2-$S(O)_z$-C(R^9R^{10})-C(R^9R^{10})-,
-O-C(O)-C(R^9R^{10})-C(R^9R^{10})-,
-C(R^9R^{10})-C(R^9R^{10})-C(O)-NR^2-,
-C(R^9R^{10})-C(R^9R^{10})-C(O)-,
-C(R^9R^{10})-NR^2-C(O)-O-,
-C(R^9R^{10})-O-C(O)-NR^2,
-C(R^9R^{10})-NR^2-C(O)-NR^2-,
-NR^2-C(O)-O-C(R^9R^{10})-,
-NR^2-C(O)-NR^2-C(R^9R^{10})-,
-NR^2-$S(O)_z$-NR^2-C(R^9R^{10})-,
-O-C(O)-NR^2-C(R^9R^{10})-,
-C(O)-N=C(R^{11})-NR^2-,
-C(O)-NR^2-C(R^{11})=N-,

$-C(R^9R^{10})-NR^{12}-C(R^9R^{10})-$,
$-NR^{12}-C(R^9R^{10})-$,
$-NR^{12}-C(R^9R^{10})-C(R^9R^{10})-$,
$-C(O)-O-C(R^9R^{10})-C(R^9R^{10})-$,
$-NR^2-C(R^{11})=N-C(O)-$,
$-C(R^9R^{10})-C(R^9R^{10})-N(R^{12})-$,
$-C(R^9R^{10})-NR^{12}-$,
$-N=C(R^{11})-NR^2-C(O)-$,
$-C(R^9R^{10})-C(R^9R^{10})-NR^2-S(O)_z-$,
$-C(R^9R^{10})-C(R^9R^{10})-S(O)_z-NR^2-$,
$-C(R^9R^{10})-C(R^9R^{10})-C(O)-O-$,
$-C(R^9R^{10})-S(O)_z-C(R^9R^{10})-$,
$-C(R^9R^{10})-C(R^9R^{10})-S(O)_z-$,
$-O-C(R^9R^{10})-C(R^9R^{10})-$,
$-C(R^9R^{10})-C(R^9R^{10})-O-$,
$-C(R^9R^{10})-C(O)-C(R^9R^{10})-$,
$-C(O)-C(R^9R^{10})-C(R^9R^{10})-$ and
$-C(R^9R^{10})-NR^2-S(O)_z-NR^2-$;

Q is a covalent bond or CH_2;

W is CH or N;

X is CR^9R^{10}, $C=CH_2$ or C=O;

Y is CR^9R^{10}, O or NR^2;

Z is C=O, C=S or $S(O)_2$;

G^1 is hydrogen, halo, hydroxy, nitro, amino, cyano, phenyl, carboxyl, $-CONH_2$, $-(C_1-C_4)$alkyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_1-C_4)$alkoxy optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_1-C_4)$alkylthio, phenoxy, $-COO(C_1-C_4)$alkyl, N,N-di-(C_1-C_4)alkylamino, $-(C_2-C_6)$alkenyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_2-C_6)$alkynyl optionally independently substituted with one or more phenyl, one or more halogens or one or more hydroxy groups, $-(C_3-C_6)$cycloalkyl optionally independently substituted with

one or more (C_1-C_4)alkyl groups, on or m re halogens or one or more hydroxy groups, -(C_1-C_4)alkylamino carbonyl or di-(C_1-C_4)alkylamino carbonyl;

G^2 and G^3 are each independently selected from the group consisting of hydrogen, halo, hydroxy, -(C_1-C_4)alkyl optionally independently substituted with one to three halo groups and -(C_1-C_4)alkoxy optionally independently substituted with one to three halo groups;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_r-A^1$, $-(CH_2)_qN(X^6)S(O)_2(CH_2)_r-A^1$, $-(CH_2)_qN(X^6)S(O)_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_r-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_r-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_r-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_r-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_r-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_r-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)S(O)_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_r-A^1$, -($C_1$-$C_{10}$)alkyl, $-(CH_2)_r-A^1$, $-(CH_2)_q$-(C_3-C_7)cycloalkyl, $-(CH_2)_q-Y^1$-(C_1-C_6)alkyl, $-(CH_2)_q-Y^1-(CH_2)_r-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_r$-(C_3-C_7)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m$(C_1-C_6)alkyl, $-CO_2$(C_1-C_4)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro groups;

Y^1 is O, $S(O)_m$, $-C(O)NX^6-$, -CH=CH-, -C≡C-, $-N(X^6)C(O)-$, $-C(O)NX^6-$, -C(O)O-, $-OC(O)N(X^6)-$ or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group in the definition of R^1 are optionally independently substituted with hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m$(C_1-C_6)alkyl, $-CO_2$(C_1-C_4)alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro groups or 1 or 2 (C_1-C_4)alkyl groups;

R^{1A} is selected from the group consisting of hydrogen, F, Cl, Br, I, (C_1-C_6)alkyl, phenyl(C_1-C_3)alkyl, pyridyl(C_1-C_3)alkyl, thiazolyl(C_1-C_3)alkyl and thienyl(C_1-C_3)alkyl, provided that R^{1A} is not F, Cl, Br or I when a heteroatom is vicinal to C";

R^2 is hydrogen, (C_1-C_8)alkyl, -(C_0-C_3)alkyl-(C_3-C_8)cycloalkyl, -(C_1-C_4)alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxy, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, -

$S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 ind pendently selected halo groups;

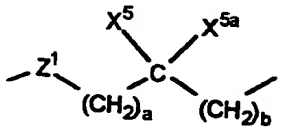
R^3 is selected from the group consisting of A^1, (C_1-C_{10})alkyl, $-(C_1-C_6)$alkyl-A^1, $-(C_1-C_6)$alkyl-(C_3-C_7)cycloalkyl, $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl, $-(C_1-C_5)$alkyl-X^1-(C_0-C_5)alkyl-A^1 and $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl-(C_3-C_7)cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 independently selected halo groups or 1, 2 or 3 independently selected $-OX^3$ groups;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_6)alkyl or (C_3-C_7)cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7)cycloalkyl, (C_5-C_7)cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6)alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are each independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, CF_3, A^1 and optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^2$, (C_3-C_7)cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylen bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylen bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then only one of X^5 or X^{5a} is on the carbon atom and only one of R^7 or R^8 is on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or N-X^2, provided that when a and b are both 0 then Z^1 is not N-X^2 or O;

R^7 and R^8 are each independently hydrogen or optionally substituted (C_1-C_6)alkyl;

where the optionally substituted (C_1-C_6)alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, -C(O)O-(C_1-C_6)alkyl, -$S(O)_m$(C_1-C_6)alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 -O-C(O)(C_1-C_{10})alkyl groups or 1 to 3 (C_1-C_6)alkoxy groups; or

R^7 and R^8 can be taken together to form -$(CH_2)_r$-L-$(CH_2)_r$-;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, fluoro, hydroxy and (C_1-C_5)alkyl optionally independently substituted with 1-5 halo groups;

R^{11} is selected from the group consisting of (C_1-C_5)alkyl and phenyl optionally substituted with 1-3 substitutents each independently selected from the group consisting of (C_1-C_5)alkyl, halo and (C_1-C_5)alkoxy;

R^{12} is selected from the group consisting of (C_1-C_5)alkylsulfonyl, (C_1-C_5)alkanoyl and (C_1-C_5)alkyl where the alkyl portion is optionally independently substituted by 1-5 halo groups;

A^1 for each occurrence is independently selected from the group consisting of (C_5-C_7)cycloalkenyl, phenyl, a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen and a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, on one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-S(O)_2N(X^6)(X^6)$, $-N(X^6)S(O)_2$-phenyl, $-N(X^6)S(O)_2X^6$, $-CONX^{11}X^{12}$, $-S(O)_2NX^{11}X^{12}$, $-NX^6S(O)_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6S(O)_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 (C_1-C_{10})alkanoyloxy groups or 1 to 3 (C_1-C_6)alkoxy groups;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, the X^{12} group is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl or optionally substituted (C_3-C_7)cycloalkyl, where the optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halo groups or 1-3 OX^3 groups;

X^3 for each occurrence is independently hydrogen or (C_1-C_6)alkyl;

X^6 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, (C_2-C_6)halogenated alkyl, optionally substituted (C_3-C_7)cycloalkyl, (C_3-C_7)-halogenated cycloalkyl, where optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^6 is optionally independently mono- or di-substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, carboxylate (C_1-C_4)alkyl ester or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6)alkyl, the two (C_1-C_6)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 as a ring member;

X^7 is hydrogen or (C_1-C_6)alkyl optionally substituted with hydroxy;

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when attached to C(O) or $S(O)_2$ in the form $C(O)X^6$, $C(O)X^{12}$, $S(O)_2X^6$ or $S(O)_2X^{12}$; and

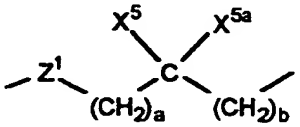
when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is independently 2 or 3.

From herein on, the word "compounds" includes a stereoisomeric mixture thereof, diastereomerically enriched, diastereomerically pure, enantiomerically

enriched or nantiomerically pure isomer thereof, or a prodrug of such comp und, mixture or isomer thereof, or a pharmaceutically acceptable salt of the compound, mixture, isomer or prodrug unless otherwise more specifically stated.

A preferred group of the foregoing compounds, designated the A Group compounds, are those compounds of formula I wherein

R^4 is hydrogen or methyl; X^4 is hydrogen;

R^6 is  where Z^1 is a bond and a is 0 or 1; X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, CF_3, phenyl and optionally substituted $(C_1\text{-}C_6)$alkyl;

where the optionally substituted $(C_1\text{-}C_6)$alkyl in the definition of X^5 and X^{5a} is optionally substituted with OX^2 or A^1;

where A^1 in the definition of X^5 and X^{5a} is imidazolyl, phenyl, indolyl, p-hydroxyphenyl, $(C_5\text{-}C_7)$cycloalkyl, $-S(O)_m(C_1\text{-}C_6)$alkyl, $-N(X^2)(X^2)$ or $-C(O)N(X^2)(X^2)$;

R^7 is hydrogen or $(C_1\text{-}C_3)$alkyl;

or X^5 and R^7 are taken together and form a $(C_1\text{-}C_5)$alkylene bridge; and

R^8 is hydrogen or $(C_1\text{-}C_3)$alkyl optionally substituted with one or two hydroxy groups.

A group of compounds which is preferred among the A Group compounds, designated the B Group, are those compounds of the A Group wherein b is 0; X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_3)$alkyl and hydroxy$(C_1\text{-}C_3)$alkyl; and

R^3 is selected from the group consisting of thienyl-CH_2-O-CH_2-, pyridyl-CH_2-O-CH_2-, thiazolyl-CH_2-O-CH_2-, 1-indolyl-CH_2-, 2-indolyl-CH_2-, 3-indolyl-CH_2-, 1-naphthyl-CH_2, 2-naphthyl-CH_2-, 1-benzimidazolyl-CH_2-, 2-benzimidazolyl-CH_2-, phenyl-$(C_1\text{-}C_4)$alkyl, 2-pyridyl-$(C_1\text{-}C_4)$alkyl-, 3-pyridyl-$(C_1\text{-}C_4)$alkyl-, 4-pyridyl-$(C_1\text{-}C_4)$alkyl-, phenyl-CH_2-S-CH_2-, thienyl-$(C_1\text{-}C_4)$alkyl-, phenyl-$(C_0\text{-}C_3)$alkyl-O-CH_2-, phenyl-CH_2-O-phenyl-CH_2-, phenyl-O-CH_2-CH_2- and 3-benzothienyl-CH_2-;

where the aryl portion(s) of the groups defined for R^3 are each optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A group of compounds which is preferred among the B Group compounds, designated the C Group, are those compounds of the B Group wherein

R^4 is hydrogen; a is 0;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, methyl or hydroxymethyl, provided that when X^5 is hydrogen then X^{5a} is not hydrogen;

R^7 and R^8 are each hydrogen; and

R^3 is selected from the group consisting of 3-indolyl-CH_2-, 1-naphthyl-CH_2-, 2-naphthyl-CH_2-, phenyl-(C_1-C_4)alkyl-, 2-pyridyl-(C_1-C_4)alkyl-, 3-pyridyl-(C_1-C_4)alkyl-, 4-pyridyl-(C_1-C_4)alkyl-, phenyl-CH_2-S-CH_2-, thienyl-(C_2-C_4)alkyl-, phenyl-(C_0-C_3)alkyl-O-CH_2-, 3-benzothienyl-CH_2-, thienyl-CH_2-O-CH_2-, thiazolyl-CH_2-O-CH_2-, pyridyl-CH_2-O-CH_2- and phenyl-O-CH_2-CH_2-;

where the aryl portion(s) of the groups defined for R^3 are each optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A group of compounds which is preferred among the C Group compounds, designated the D Group, are those compounds of the C Group wherein

R^1 is -$(CH_2)_t$-A^1, -$(CH_2)_q$-(C_3-C_7)cycloalkyl or (C_1-C_{10})alkyl;

A^1 in the definition of R^1 is phenyl, pyridyl, thiazolyl or thienyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3;

the cycloalkyl and alkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy or 1 to 3 fluoro atoms;

q is 1 or 2; t is 1 or 2;

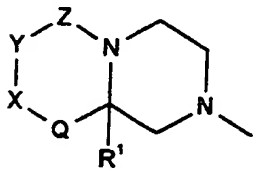
R^3 is phenyl-CH_2-O-CH_2-, phenyl-CH_2-S-CH_2-, pyridyl-CH_2-O-CH_2-, thienyl-CH_2-O-CH_2-, thiazolyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$- or 3-indolyl-CH_2-;

where the carbon atom bearing the substituent R^3 is of the (R)-configuration;

where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3; and

X^5 and X^{5a} are each methyl.

A group of compounds which is preferred among the D Group compounds, designated the E Group, are those compounds of the D Group wherein HET is



A group of compounds which is preferred among the E Group compounds, designated the F Group, are those compounds of the E Group wherein

Z is $S(O)_2$; Q is a covalent bond; X is CH_2; and

Y is CH_2 or NR^2;

R^2 is hydrogen, $(C_1\text{-}C_5)$alkyl or $\text{-}(C_0\text{-}C_2)$alkyl-$(C_3\text{-}C_8)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^2 are optionally substituted with 1, 2 or 3 fluoro groups.

A group of compounds which is preferred among the F Group compounds, designated the G Group, are those compounds of the F Group wherein Y is CH_2.

A group of compounds which is preferred among the G Group compounds, designated the H Group, are those compounds of the G Group wherein

R^1 is $\text{-}CH_2\text{-}A^1$ where A^1 is phenyl, pyridyl or thiazolyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3; and

R^3 is selected from the group consisting of 3-indolyl-CH_2-, phenyl-$(CH_2)_3$-, phenyl-CH_2-O-CH_2- and thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A preferred compound of the H Group is the 3a(R,S),1(R) diastereomeric mixture, the 3a(R),1(R) diastereomer or the 3a(S),1(R) diastereomer of 2-amino-N-[2-(3a-benzyl-1,1-dioxo-hexahydro-1-thia-5,7a-diaza-inden-5-yl)-1-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide.

Another group of compounds which is preferred among the E Group compounds, designated th I Group, are those compounds of the E Group wherein

Z is C=O; Q is a covalent bond; X is CH_2; and Y is NR^2;

R^2 is hydrogen, (C_1-C_5)alkyl or $-(C_0-C_2)$alkyl-(C_3-C_8)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^2 are optionally substituted with 1, 2 or 3 fluoro groups.

A group of compounds which is preferred among the I Group compounds, designated the J Group, are those compounds of the I Group wherein

R^1 is $-CH_2-A^1$ where A^1 is phenyl, pyridyl or thiazolyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3;

R^2 is hydrogen or (C_1-C_3)alkyl optionally substituted with 1-3 fluoro groups; and

R^3 is selected from the group consisting of 3-indolyl-CH_2-, phenyl-$(CH_2)_3$-, phenyl-CH_2-O-CH_2-and thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A preferred compound of the J Group is the 8a(R,S),1(R) diastereomeric mixture, the 8a(R),1(R) diastereomer or the 8a(S),1(R) diastereomer of 2-amino-N-[2-(8a-benzyl-2-methyl-3-oxo-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-1-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide.

Another group of compounds which is preferred among the E Group compounds, designated the K Group, are those compounds of the E Group wherein Z is C=O; Q is a covalent bond; X is CH_2; and Y is O.

A group of compounds which is preferred among the K Group compounds, designated the L Group, are those compounds of the K Group wherein

R^1 is $-CH_2-A^1$ where A^1 is phenyl, pyridyl or thiazolyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3; and

R^3 is selected from the group consisting of 3-indolyl-CH_2-, phenyl-$(CH_2)_3$-, phenyl-CH_2-O-CH_2- and thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A group of compounds which is preferred among the L Group compounds, designated th M Group, are where the compound is the 8a(R,S),1(R) diastereomeric mixture, the 8a(R),1(R) diastereomer or the 8a(S),1(R) diastereomer of the compound selected from the group consisting of

2-amino-N-[2-(8a-benzyl-3-oxo-tetrahydro-oxazolo[3,4-a]pyrazin-7-yl)-1-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide,

2-amino-N-[1-benzyloxymethyl-2-oxo-2-(3-oxo-8a-thiazol-4-ylmethyl-tetrahydro-oxazolo[3,4-a]pyrazin-7-yl)-ethyl]-2-methyl-propionamide and

2-amino-N-[1-benzyloxymethyl-2-oxo-2-(3-oxo-8a-pyridin-3-ylmethyl-tetrahydro-oxazolo[3,4-a]pyrazin-7-yl)-ethyl]-2-methyl-propionamide.

Another group of compounds which is preferred among the E Group compounds, designated the N Group, are those compounds of the E Group wherein Z is C=O or $S(O)_2$; Q is a covalent bond; X is C=O; and Y is NR^2;

R^2 is hydrogen, (C_1-C_5)alkyl or $-(C_0-C_2)$alkyl-(C_3-C_8)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^2 are optionally substituted with 1, 2 or 3 fluoro groups.

A group of compounds which is preferred among the N Group compounds, designated the O Group, are those compounds of the N Group wherein Z is C=O; R^1 is $-CH_2-A^1$, where A^1 in the definition of R^1 is phenyl or pyridyl where said phenyl or pyridyl is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3; and

R^3 is phenyl-CH_2-O-CH_2-, pyridyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$-, 3-indolyl-CH_2- or thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A group of compounds which is preferred among the O Group compounds, designated the P Group, are those compounds of the O Group wherein R^2 is hydrogen or (C_1-C_3)alkyl where the alkyl group is optionally substituted with 1-3 fluoro groups.

A group of compounds which is preferred among the P Group compounds, designated the Q Group, are those compounds of the P Group wh rein

R^3 is phenyl-CH_2-O-CH_2- or ph nyl-$(CH_2)_3$-, where the phenyl in the definition of R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A group of compounds which is preferred among the Q Group compounds, designated the R Group, are those compounds of the Q Group wherein

R^1 is -CH_2-A^1 where A^1 is phenyl, 2-pyridyl, 3-pyridyl, optionally substituted with 1-3 fluoro groups or 1-3 Chloro groups;

R^2 is methyl or ethyl where the ethyl group is optionally substituted with 1-3 fluoro groups; and

R^3 is phenyl-CH_2-O-CH_2-, where the phenyl is optionally substituted with 1-3 fluoro groups, 1-3 Chloro groups or 1-2 CF_3 groups.

A preferred compound of the R Group is the 1(R),8a(R,S) diastereomeric mixture, the 1(R),8a(R) diastereomer or the 1(R),8a(S) diastereomer of 2-amino-N-{1-(2,4-difluoro-benzyloxymethyl)-2-[1,3-dioxo-8a-pyridin-3-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide.

A group of compounds which is preferred among the R Group compounds, designated the S Group, are those compounds of the R Group wherein

R^1 is -CH_2-A^1 where A^1 is phenyl optionally substituted with 1-2 chloro groups or 1-2 fluoro groups;

R^2 is methyl or -CH_2CF_3; and

R^3 is phenyl-CH_2-O-CH_2-, optionally substituted with 1-3 fluoro groups, 1-3 chloro groups or 1-2 CF_3 groups.

A group of compounds which is preferred among the S Group compounds, designated the T Group, are those compounds of the S Group where the compound is selected from the group consisting of

2-amino-N-[2-(8a-(R,S)-benzyl-2-methyl-1,3-dioxo-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide,

2-amino-N-{1-(R)-benzyloxymethyl-2-[8a-(R,S)-(4-fluoro-benzyl)-2-methyl-1,3-dioxo-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide and

2-amino-N-{2-[8a-(R,S)-benzyl-1,3-dioxo-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl}-2-methyl-propionamide.

The following compounds are particularly preferred of the T Group compounds:

2-amino-N-[2-(8a-(R)-benzyl-2-methyl-1,3-dioxo-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide;

2-amino-N-[2-(8a-(S)-benzyl-2-methyl-1,3-dioxo-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide;

2-amino-N-{1-(R)-benzyloxymethyl-2-[8a-(R)-(4-fluoro-benzyl)-2-methyl-1,3-dioxo-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide;

2-amino-N-{1-(R)-benzyloxymethyl-2-[8a-(S)-(4-fluoro-benzyl)-2-methyl-1,3-dioxo-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide;

2-amino-N-{2-[8a-(R)-benzyl-1,3-dioxo-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl}-2-methyl-propionamide; and

2-amino-N-{2-[8a-(S)-benzyl-1,3-dioxo-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl}-2-methyl-propionamide.

Another group of compounds which is preferred among the R Group compounds, designated the U Group, are those compounds of the R Group wherein R^1 is $-CH_2-A^1$ where A^1 is 2-pyridyl optionally substituted with 1-2 chloro groups;
R^2 is methyl or $-CH_2CF_3$; and
R^3 is phenyl-CH_2-O-CH_2-, optionally substituted with 1-3 fluoro groups, 1-3 chloro groups or 1-2 CF_3 groups.

A group of compounds which is preferred among the U Group compounds, designated the V Group, are those compounds of the U Group where the compound is

2-amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-1,3-dioxo-8a-(R,S)-pyridin-2-ylmethyl-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethyl]-2-methyl-propionamide,

2-amino-N-{1-(R)-benzyloxymethyl-2-[1,3-dioxo-8a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide,

2-amino-N-{1-(R)-(2,4-difluoro-benzyloxymethyl)-2-[1,3-dioxo-8a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide,

2-amino-N-[2-[1,3-dioxo-8a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-1-(R)-(2-trifluoromethyl-benzyloxymethyl)-ethyl]-2-methyl-propionamide or

2-amino-N-{1-(R)-(4-chloro-benzyloxymethyl)-2-[1,3-dioxo-8a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide.

The following compounds are particularly preferred of the V Group compounds:

2-amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-1,3-dioxo-8a-(R)-pyridin-2-ylmethyl-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethyl]-2-methyl-propionamide;

2-amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-1,3-dioxo-8a-(S)-pyridin-2-ylmethyl-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethyl]-2-methyl-propionamide;

2-amino-N-{1-(R)-benzyloxymethyl-2-[1,3-dioxo-8a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide;

2-amino-N-{1-(R)-benzyloxymethyl-2-[1,3-dioxo-8a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide;

2-amino-N-{1-(R)-(2,4-difluoro-benzyloxymethyl)-2-[1,3-dioxo-8a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide;

2-amino-N-{1-(R)-(2,4-difluoro-benzyloxymethyl)-2-[1,3-dioxo-8a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide;

2-amino-N-[2-[1,3-dioxo-8a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-1-(R)-(2-trifluoromethyl-benzyloxymethyl)-ethyl]-2-methyl-propionamide;

2-amino-N-[2-[1,3-dioxo-8a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-1-(R)-(2-trifluoromethyl-benzyloxymethyl)-ethyl]-2-methyl-propionamide;

2-amino-N-{1-(R)-(4-chloro-b nzyloxymethyl)-2-[1,3-dioxo-8a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-m thyl-propionamide; and

2-amino-N-{1-(R)-(4-chloro-benzyloxymethyl)-2-[1,3-dioxo-8a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide.

Another group of compounds which is preferred among the E Group compounds, designated the W Group, are those compounds of the E Group wherein

Z is C=O; Q is a covalent bond; X is C=O; and Y is CH_2.

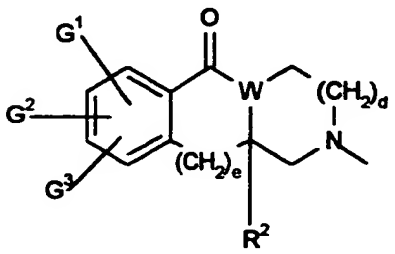
A group of compounds which is preferred among the W Group compounds, designated the X Group, are those compounds of the W Group wherein

R^1 is $-CH_2-A^1$ where A^1 is phenyl, pyridyl or thiazolyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of fluoro, chloro, methyl, OCH_3, OCF_2H, OCF_3 and CF_3; and

R^3 is selected from the group consisting of 3-indolyl-CH_2-, phenyl-$(CH_2)_3$-, phenyl-CH_2-O-CH_2- and thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A preferred compound of the X Group is the 1(R), 8a(R,S) diastereomeric mixture, the 1(R),8a(R) diastereomer or the 1(R),8a(S) diastereomer of 2-amino-N-{1-benzyloxymethyl-2-[8a-(4-fluoro-benzyl)-6,8-dioxo-hexahydro-pyrrolo [1,2-a]pyrazin-2-yl]-2-oxo-ethyl}-2-methyl-propionamide.

Another group of compounds which is preferred among the D Group compounds, designated the Y Group, are those compounds of the D Group wherein HET is



A group of compounds which is preferred among the Y Group compounds, designated th Z Group, are those compounds of th Y Group wherein

W is N; d is 1; e is 0 or 1;

R^2 is hydrogen, $(C_1\text{-}C_5)$alkyl or $-(C_0\text{-}C_2)$alkyl-$(C_3\text{-}C_8)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^2 are optionally substituted with 1, 2 or 3 fluoro groups;

G^1 is hydrogen, halo, hydroxy, $-(C_1\text{-}C_2)$alkyl optionally independently substituted with one to three halo groups or $-(C_1\text{-}C_2)$alkoxy optionally independently substituted with one to three halo groups;

G^2 is hydrogen, halo, hydroxy, $-(C_1\text{-}C_2)$alkyl optionally independently substituted with one to three halo groups or $-(C_1\text{-}C_2)$alkoxy optionally independently substituted with one to three halo groups; and

G^3 is hydrogen.

A group of compounds which is preferred among the Z Group compounds, designated the AA Group, are those compounds of the Z Group wherein

R^2 is hydrogen or $(C_1\text{-}C_3)$alkyl optionally substituted with 1-3 fluoro groups;

R^3 is selected from the group consisting of 3-indolyl-CH_2-, phenyl-$(CH_2)_3$-, phenyl-CH_2-O-CH_2- and thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3; and

G^1, G^2 and G^3 are each independently hydrogen, Cl or F.

A preferred compound of the AA Group is 2-amino-N-[1-(R)-(1H-indol-3-ylmethyl)-2-oxo-2-(9-oxo-1,2,4a,9-tetrahydro-4H-3,9a-diaza-fluoren-3-yl)-ethyl]-2-methyl-propionamide.

Another group of compounds which is preferred among the C Group compounds, designated the AB Group, are those compounds of the C Group wherein

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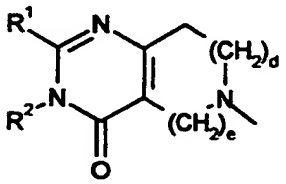

A group of compounds which is preferred among the AB Group compounds, designated the AC Group, are those compounds of the AB Group wherein

X^5 and X^{5a} are each methyl; d is 1; e is 1;

R^1 is $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl or (C_1-C_{10})alkyl;

A^1 in the definition of R^1 is phenyl, pyridyl, thiazolyl or thienyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3;

the cycloalkyl and alkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy or 1 to 3 fluoro groups;

t is 1 or 2; q is 1 or 2; and

R^2 is hydrogen, (C_1-C_5)alkyl or $-(C_0-C_2)$alkyl-(C_3-C_8)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^2 are optionally substituted with 1, 2 or 3 fluoro groups.

A group of compounds which is preferred among the AC Group compounds, designated the AD Group, are those compounds of the AC Group wherein

R^1 is (C_1-C_6)alkyl optionally substituted with 1-3 fluoro groups;

R^2 is hydrogen or (C_1-C_3)alkyl optionally substituted with 1-3 fluoro groups; and

R^3 is selected from the group consisting of 3-indolyl-CH_2-, phenyl-$(CH_2)_3$-, phenyl-CH_2-O-CH_2- and thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A preferred compound of the AD Group is 2-amino-N-[2-(2,3-dimethyl-4-oxo-3,5,7,8-tetrahydro-4H-pyrido[4,3-d]pyrimidin-6-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-propionamide.

Another group of compounds which is preferred among the D Group compounds, designated the AE Group, are those compounds of the D Group wherein

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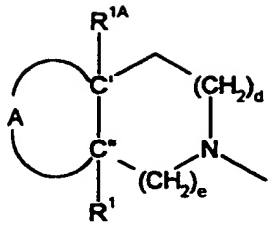


A group of compounds which is preferred among the AE Group compounds, designated the AF Group, are those compounds of the AE Group wherein

A is $-NR^2-C(O)-O-$; d is 1; e is 1;

R^1 is $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl or (C_1-C_{10})alkyl;

A^1 in the definition of R^1 is phenyl, pyridyl, thiazolyl or thienyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3;

the cycloalkyl and alkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy or 1-3 fluoro groups;

t is 1 or 2; q is 1 or 2;

R^{1A} is hydrogen or methyl; and

R^2 is hydrogen, (C_1-C_5)alkyl, $-(C_0-C_2)$alkyl-(C_3-C_8)cycloalkyl or (C_1-C_2)alkyl-A^1, where A^1 in the definition of R^2 is pyridyl;

where the alkyl and cycloalkyl groups in the definition of R^2 are optionally substituted with 1-3 fluoro groups.

A group of compounds which is preferred among the AF Group compounds, designated the AG Group, are those compounds of the AF Group wherein

R^1 is $-CH_2-A^1$ where A^1 is phenyl, pyridyl or thiazolyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3;

R^2 is hydrogen or (C_1-C_3)alkyl optionally substituted with 1-3 fluoro groups;

R^3 is selected from the group consisting of 3-indolyl-CH_2-, phenyl-$(CH_2)_3-$, phenyl-CH_2-O-CH_2- and thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3; and

R^{1A} is hydrogen.

A group of compounds which is preferred among the AG Group compounds, designated the AH Group, are those compounds of the AG Group wherein the compound is the 3a(R,S)-7a(R,S) diastereomeric mixture, the 3a(R),7a(R) diastereomer, the 3a(S),7a(S) diastereomer, the 3a(R),7a(S) diastereomer or the 3a(S),7a(R) diastereomer of the compound selected from the group consisting of 3a-7a-2-amino-N-[2-(3a-benzyl-2-oxo-hexahydro-oxazolo[4,5-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide, 3a-7a-2-amino-N-[1-(R)-benzyloxymethyl-2-(3-methyl-2-oxo-3a-pyridin-3-ylmethyl-hexahydro-oxazolo[4,5-c]pyridin-5-yl)-2-oxo-ethyl]-2-methyl-propionamide, 3a-7a-2-amino-N-[2-(3a-benzyl-3-methyl-2-oxo-hexahydro-oxazolo[4,5-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-propionamide and 3a-7a-2-amino-N-[1-(R)-benzyloxymethyl-2-oxo-2-(2-oxo-3a-pyridin-2-ylmethyl-hexahydro-oxazolo[4,5-c]pyridin-5-yl)-ethyl]-2-methyl-propionamide.

Another group of compounds which is preferred among the AE Group compounds, designated the AI Group, are those compounds of the AE Group wherein

A is $-C(O)-NR^2-CH_2-$, $-C(O)-O-CH_2-$, $-C(O)-NR^2-C(O)-$, $-CH_2-NR^{12}-CH_2-$ or $-C(O)-NR^2-CH_2-CH_2-$;

d is 1; e is 1;

R^1 is $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl or (C_1-C_{10})alkyl;

A^1 in the definition of R^1 is phenyl, pyridyl, thiazolyl or thienyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3;

the cycloalkyl and alkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy or 1-3 fluoro groups;

t is 1 or 2; q is 1 or 2;

R^{1A} is hydrogen or methyl; and

R^2 is hydrogen, (C_1-C_5)alkyl, $-(C_0-C_2)$alkyl-(C_3-C_8)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^2 are optionally substituted with 1-3 fluoro groups.

A group of compounds which is preferred among the AI Group compounds, designated the AJ Group, are those compounds of the AI Group wherein

R^1 is $-CH_2-A^1$ where A^1 is phenyl, pyridyl or thiazolyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3;

R^2 is hydrogen or (C_1-C_3)alkyl optionally substituted with 1-3 fluoro groups; and

R^3 is selected from the group consisting of 3-indolyl-CH_2-, phenyl-$(CH_2)_3$-, phenyl-CH_2-O-CH_2- and thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3; and

R^{1A} is hydrogen.

A group of compounds which is preferred among the AJ Group compounds, designated the AK Group, are those compounds of the AJ Group where the compound is selected from the group consisting of

2-amino-N-[1-(R)-(1H-indol-3-ylmethyl)-2-(2-methyl-1,3-dioxo-octahydro-pyrrolo[3,4-c]pyridin-5-yl)-2-oxo-ethyl]-2-methyl-propionamide,

the 3a(R,S),1(R) diastereomeric mixture, the 3a(R),1(R) diastereomer or the 3a(S),1(R) diastereomer of 2-amino-N-[2-(3a-benzyl-3-oxo-octahydro-pyrrolo[3,4-c]pyridin-5-yl)-1-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide,

the 3a(R,S),1(R) diastereomeric mixture, the 3a(R),1(R) diastereomer or the 3a(S),1(R) diastereomer of 2-amino-N-[2-(3a-benzyl-3-oxo-hexahydro-furo[3,4-c]pyridin-5-yl)-1-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide,

the 3a(R,S),1(R) diastereomeric mixture, the 3a(R),1(R) diastereomer or the 3a(S),1(R) diastereomer of N-[2-(2-acetyl-3a-benzyl-octahydro-pyrrolo[3,4-c]pyridin-5-yl)-(1H-indol-2-ylmethyl)-2-oxo-ethyl]-2-amino-2-methyl-propionamide and

the 8a(R,S),1(R) diastereomeric mixture, the 8a(R),1(R) diastereomer or the 8a(S),1(R) diastereomer of 2-amino-N-[2-(8a-benzyl-7-methyl-8-oxo-octahydro-[2,7]naphthyridin-2-yl)-1-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide.

Another group of compounds which is preferred among the AE Group compounds, designated the AL Group, are those compounds of the AE Group wherein

R^1 is $-(CH_2)_r-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl or (C_1-C_{10})alkyl;

A^1 in the definition of R^1 is phenyl, pyridyl, thiazolyl or thienyl, optionally substituted with one to three substituents, each substituent being

independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3;

the cycloalkyl and alkyl groups in the definition of R^1 are optionally substituted with $(C_1$-$C_4)$alkyl, hydroxy, $(C_1$-$C_4)$alkoxy, or 1-3 fluoro groups;

t is 1 or 2; q is 1 or 2;

R^{1A} is hydrogen or methyl;

R^2 is hydrogen, $(C_1$-$C_5)$alkyl or -$(C_0$-$C_2)$alkyl-$(C_3$-$C_8)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^2 are optionally substituted with 1-3 fluoro groups;

d is 1; e is 1; and

R^9 and R^{10} are each hydrogen.

A group of compounds which is preferred among the AL Group compounds, designated the AM Group, are those compounds of the AL Group wherein

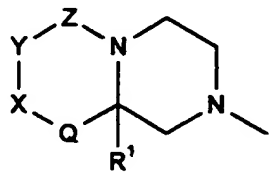
R^1 is -CH_2-A^1 where A^1 is phenyl, pyridyl or thiazolyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3;

R^2 is hydrogen or $(C_1$-$C_3)$alkyl optionally substituted with 1-3 fluoro groups; and

R^3 is selected from the group consisting of 3-indolyl-CH_2-, phenyl-$(CH_2)_3$-, phenyl-CH_2-O-CH_2- and thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3; and

R^{1A} is hydrogen.

Another group of compounds which is preferred among the C Group compounds, designated the AN Group, are those compounds of the C Group wherein

HET is 

;

Z is C=O or $S(O)_2$; Q is a covalent bond; X is C=O; Y is NR^2;

R^2 is hydrogen, (C_1-C_5)alkyl or $-(C_0-C_2)$alkyl-(C_3-C_8)cycloalkyl; where the alkyl and cycloalkyl groups in the definition of R^2 are optionally substituted with 1, 2 or 3 fluoro groups;

R^1 is hydrogen; and

R^3 is selected from the group consisting of phenyl-CH_2-O-CH_2-, pyridyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$-, 3-indolyl-CH_2- and thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A group of compounds which is preferred among the AN Group compounds, designated the AO Group, are those compounds of the AN Group wherein Z is C=O; R^2 is hydrogen or (C_1-C_3)alkyl optionally substituted with 1-3 fluoro groups.

A group of compounds which is preferred among the AO Group compounds, designated the AP Group, are those compounds of the AO Group wherein R^3 is selected from the group consisting of 3-indolyl-CH_2-, phenyl-$(CH_2)_3$-, phenyl-CH_2-O-CH_2- and thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A preferred compound of the AP Group is 8a-(R,S)-2-amino-N-[1-(R)-(1H-indol-3-ylmethyl)-2-(2-methyl-1,3-dioxo-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethyl]-2-methyl-propionamide.

An even more preferred compound of the AP Group is 8a-(R)-2-amino-N-[1-(R)-(1H-indol-3-ylmethyl)-2-(2-methyl-1,3-dioxo-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethyl]-2-methyl-propionamide.

Another more preferred compound of the AP Group is 8a-(S)-2-amino-N-[1-(R)-(1H-indol-3-ylmethyl)-2-(2-methyl-1,3-dioxo-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethyl]-2-methyl-propionamide.

This invention also provides:

methods for increasing levels of endogenous growth hormone in a human or other animal such as especially dogs, cats and horses, which comprise administering to such human or other animal an effective amount of a compound of Formula I;

pharmaceutical compositions which comprise a pharmaceutically acceptabl carrier and an effective amount of a compound of Formula I;

pharmaceutical compositions useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprise a pharmaceutically acceptable carrier, an effective amount of a compound of Formula I and a growth hormone secretagogue selected from the group consisting of GHRP-6, Hexarelin, GHRP-1, growth hormone releasing factor (GRF), IGF-1, IGF-2 and B-HT920 or an analog thereof;

methods for treating or preventing osteoporosis and/or frailty which comprise administering to a human or other animal especially dogs, cats and horses, in need of such treatment or prevention an amount of a compound of Formula I which is effective in treating or preventing osteoporosis and/or frailty;

methods for treating or preventing diseases or conditions which may be treated or prevented by growth hormone which comprise administering to a human or other animal in need of such treatment or prevention an amount of a compound of Formula I which is effective in promoting release of endogenous growth hormone;

preferred methods of the immediately foregoing methods is where the disease or condition is congestive heart failure, frailty associated with aging or obesity;

preferred methods of the immediately foregoing methods is where the disease or condition is congestive heart failure or frailty associated with aging;

methods for accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness such as AIDS or cancer, accelerating wound healing, or accelerating the recovery of burn patients or patients having undergone major surgery, which methods comprise administering to a mammal in need of such treatment an amount of a compound of Formula I which is effective in promoting release of endogenous growth hormone;

preferred methods of the immediately foregoing methods is for accelerating the recovery of patients having undergone major surgery or for accelerating bone fracture repair;

methods for improving muscle strength, mobility, maintenance of skin thickness, metabolic h meostasis or renal homeostasis, which methods comprise

administering to a human or other animal in need of such treatment an amount of a compound of Formula I which is effectiv in promoting release of endogenous growth hormone;

methods for the treatment or prevention of osteoporosis and/or frailty which comprises administering to a human or other animal especially dogs, cats and horses, with osteoporosis and/or frailty effective amounts of a bisphosphonate compound and a compound of Formula I;

preferred methods of the immediately foregoing methods is where the bisphosphonate compound is alendronate or ibandronate;

methods for the treatment or prevention of osteoporosis and/or frailty which comprise administering to a human or other animal especially dogs, cats and horses, with osteoporosis and/or frailty effective amounts of estrogen or Premarin® and a compound of Formula I and, optionally, progesterone;

methods for the treatment of osteoporosis and/or frailty which comprise administering to a human or other animal especially dogs, cats and horses, with osteoporosis and/or frailty effective amounts of calcitonin and a compound of Formula I;

methods to increase IGF-1 levels in a human or other animal especially dogs, cats and horses, deficient in IGF-1 which comprise administering to a human or other animal with IGF-1 deficiency a compound of Formula I;

methods for the treatment of osteoporosis and/or frailty which comprises administering to a human or other animal especially dogs, cats and horses, with osteoporosis and/or frailty effective amounts of an estrogen agonist or antagonist and a compound of Formula I;

preferred methods of the immediately foregoing methods is where the estrogen agonist or antagonist is tamoxifen, droloxifene, raloxifene, idoxifene, *cis*-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; (-)-*cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; *cis*-1-[6'-pyrrolodinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydro-naphthalene; 1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; *cis*-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-pyrrolidinolethoxyph nyl)-2-ph nyl-6-hydroxy-1,2,3,4-tetrahydro-isoquinoline.

methods for enhancing growth and improving carcass quality of an animal other than humans which comprise administering to said animal an effective amount of a compound of Formula I;

methods for enhancing feed efficiency in an animal other than humans which comprise administering to said animal an effective amount of a compound of Formula I;

methods for increasing milk production in a female mammal which comprise administering to said female mammal an effective amount of a compound of Formula I;

methods for increasing piglet number, increasing pregnancy rate in sows, increasing viability of piglets, increasing weight of piglets or increasing muscle fiber size in piglets which comprise administering to a sow or piglet an effective amount of a compound of Formula I;

methods for increasing muscle mass, which comprise administering to a human or other animal such as dogs, cats, horses, cattle, pigs, chickens, turkeys, sheep and fish, in need of such treatment an amount of a compound of Formula I;

methods for promoting growth in growth hormone deficient children which comprise administering to a growth hormone deficient child a compound of Formula I;

methods for the treatment or prevention of congestive heart failure, obesity or frailty associated with aging, which comprise administering to a human or other animal in need thereof effective amounts of a functional somatostatin antagonist and a compound of Formula I;

preferred methods of the immediately foregoing methods is where the functional somatostatin antagonist is an alpha-2 adrenergic agonist and the other animal is a dog, cat or a horse;

preferred methods of the immediately foregoing methods is where the alpha-2 adrenergic agonist is clonidine, xylazine or medetomidine.

methods for treating insulin resistance in a mammal, which comprises administering to said mammal an effective amount of a compound of Formula I;

preferred methods of the immediately foregoing methods is where the condition associated with insulin resistance is type I diabetes, type II diabetes,

hyperglycemia, impaired glucos tolerance or an insulin resistant syndrome; or where th condition associated with insulin resistance is associated with obesity or old age;

methods for increasing the endogenous production or release of growth hormone in a human or other animal especially dogs, cats and horses, which comprise administering effective amounts of a compound of Formula I and a growth hormone secretagogue selected from the group consisting of GHRP-6, Hexarelin, GHRP-1, growth hormone releasing factor (GRF), IGF-1, IGF-2 and B-HT920 or an analog thereof;

pharmaceutical compositions useful for treating or preventing osteoporosis and/or frailty which comprise a pharmaceutically acceptable carrier, an amount of a bisphosphonate compound and an amount of a compound of Formula I;

pharmaceutical compositions useful for treating or preventing osteoporosis and/or frailty which comprises a pharmaceutically acceptable carrier, an amount of estrogen or Premarin®, an amount of a compound of Formula I and, optionally, an amount of progesterone;

pharmaceutical compositions useful for treating osteoporosis and/or frailty which comprise a pharmaceutically acceptable carrier, an amount of calcitonin and an amount of a compound of Formula I;

pharmaceutical compositions useful for treating preventing congestive heart failure, obesity or frailty associated with aging, which comprise a pharmaceutically acceptable carrier, an amount of an alpha-2 adrenergic agonist and an amount of a compound of Formula I;

a preferred pharmaceutical composition of the immediately foregoing compositions is where the alpha-2 adrenergic agonist is clonidine, xylazine or medetomidine; and

methods for increasing levels of endogenous growth hormone, which comprise administering to a human or other animal in need thereof effective amounts of a functional somatostatin antagonist and a compound of Formula I.

In yet another aspect, this invention provides methods for improving muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis and renal homeostasis, which comprise administering to a human or other animal especially

dogs, cats and horses, in need of such treatment an amount of a comp und of claim 1 which is effective in promoting release of endogenous growth hormone.

The instant compounds promote the release of growth hormone which are stable under various physiological conditions and may be administered parenterally, nasally or by the oral route.

Another group of compounds which is preferred within the E Group compounds, designated the EA Group, comprises those compounds, or stereoisomeric mixtures thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers thereof, or prodrugs of such compounds, mixtures or isomers thereof, or pharmaceutically acceptable salts of the compounds, mixtures, isomers or prodrugs wherein:

Z is C=O; Q is a covalent bond;

Y is CR^9R^{10}

where R^9 in the definition of Y is selected from the group consisting of hydrogen, fluoro, hydroxy and (C_1-C_2)alkyl optionally substituted with 1-3 fluoro groups; and R^{10} in the definition of Y is selected from the group consisting of hydrogen, fluoro, and (C_1-C_2)alkyl optionally substituted with 1-3 fluoro groups with the proviso that R^{10} cannot be fluoro when R^9 is hydroxy;

and X is CHR^9

where R^9 in the definition of X is selected from the group consisting of hydrogen, fluoro, hydroxy and (C_1-C_2)alkyl optionally substituted with 1-3 fluoro groups.

A group of compounds which is preferred within the EA Group compounds, designated the EB Group, comprises those compounds or stereoisomeric mixtures thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers thereof, or prodrugs of such compounds, mixtures or isomers thereof, or pharmaceutically acceptable salts of the compounds, mixtures, isomers or prodrugs wherein:

R^1 is $-CH_2-A^1$ where A^1 is phenyl, pyridyl or thiazolyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3; and

R^3 is selected form the group consisting f 3-indolyl-CH_2-, phenyl-$(CH_2)_3$-, ph nyl-CH_2-O-CH_2- and thiazolyl-CH_2-O-CH_2-, where the aryl p rtion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3.

A group of compounds which is preferred within the EB Group compounds, designated the EC Group, comprises those compounds or stereoisomeric mixtures thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers thereof, or prodrugs of such compounds, mixtures or isomers thereof, or pharmaceutically acceptable salts of the compounds, mixtures, isomers or prodrugs wherein

X is CH_2;

Y is CR^9R^{10}

where R^9 and R^{10} in the definition of Y are independently selected from the group consisting of hydrogen, fluoro, and $(C_1$-$C_2)$alkyl optionally substituted with 1-3 fluoro groups.

A group of compounds which is preferred within the EC Group, designated the ED Group, comprises those compounds or prodrugs of such compounds or pharmaceutically acceptable salts of the compounds or prodrugs wherein the compound is the 8a(R,S),1(R) diastereomeric mixture, the 8a(R),1(R) diastereomer or the 8a(S),1(R) diastereomer of 2-amino-N-[2-(8a-benzyl-6-oxo-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-1-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide or 2-amino-N-[1-benzyloxymethyl-2-oxo-2-(6-oxo-8a-pyridin-2-ylmethyl-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-ethyl]-2-methyl-propionamide.

Another group of compounds which is preferred within the J Group comprises those compounds or prodrugs of such compounds or pharmaceutically acceptable salts of the compounds or prodrugs wherein the compound is the 8a(R,S),1(R) diastereomeric mixture, the 8a(R),1(R) diastereomer or the 8a(S),1(R) diastereomer of 2-amino-N-{1-benzyloxymethyl-2-oxo-2-[3-oxo-8a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-ethyl}-2-methyl-propionamide; 2-amino-N-{1-benzyloxymethyl-2-[8a-(2,4-difluoro-benzyl)-3-oxo-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide; 2-amino-N-[1-benzyloxym thyl-2-oxo-2-(3-oxo-8a-pyridin-2-

ylmethyl-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-ethyl]-2-methyl-propionamide; or 2-amino-N-[1-benzyloxymethyl-2-(2-ethyl-3-oxo-8a-pyridin-2-ylmethyl-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethyl]-2-methyl-propionamide.

Another group of compounds which is preferred within the Q Group compounds, designated the QA Group, comprises those compounds or stereoisomeric mixtures thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers thereof, or prodrugs of such compounds, mixtures or isomers thereof, or pharmaceutically acceptable salts of the compounds, mixtures, isomers or prodrugs wherein:

R^1 is $-CH_2-A^1$ where A^1 is phenyl, 2-pyridyl, or 3-pyridyl, optionally substituted with 1-3 F, 1-3 Cl;

R^2 is methyl or ethyl where the ethyl group is optionally substituted with 1-3 F; and

R^3 is phenyl-$(CH_2)_{3-}$, where the phenyl is optionally substituted with 1-3 F, 1-3 Cl or 1-2 CF_3;

A group of compounds which is preferred within the QA Group of compounds, designated the QB Group, comprises those compounds or stereoisomeric mixtures thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers thereof, or prodrugs of such compounds, mixtures or isomers thereof, or pharmaceutically acceptable salts of the compounds, mixtures, isomers or prodrugs wherein R^1 is $-(CH_2)-A^1$ where A^1 is 2-pyridyl, optionally substituted with 1-2 Cl; and

R^2 is methyl or $-CH_2CF_3$.

A group of compounds which is preferred within the QB Group of compounds, designated the QC Group, comprises those compounds or prodrugs of such compounds or pharmaceutically acceptable salts of the compounds or prodrugs wherein the compound is 2-amino-N-{1-(R)-[1,3-dioxo-8a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazine-7-carbonyl]-(4-phenyl-butyl)}-2-methyl-propionamide.

An especially preferred compound within the QC Group comprises the compound or prodrugs of such compound or pharmaceutically acceptable salts of the compound or prodrugs where the compound is 2-amino-N-{1-(R)-[1,3-dioxo-8a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazine-7-carbonyl]-(4-phenyl-butyl)}-2-methyl-propionamide.

Another especially preferred compound within the QC Group compris s the comp und or prodrugs of such compound or pharmaceutically acceptable salts of the compound or prodrugs where the compound is 2-amino-N-{1-(R)-[1,3-dioxo-8a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazine-7-carbonyl] -(4-phenyl-butyl)}-2-methyl-propionamide.

Another group of compounds which is preferred within the AI Group of compounds, designated the AI^A Group, comprises those compounds or stereoisomeric mixtures thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers thereof, or prodrugs of such compounds, mixtures or isomers thereof, or pharmaceutically acceptable salts of the compounds, mixtures, isomers or prodrugs wherein:

A is $-C(O)-NR^2-CH_2-$;

R^1 is $-CH_2-A^1$ where A^1 is phenyl, pyridyl or thiazolyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3;

R^2 is hydrogen or $-(C_1-C_3)$alkyl or $-(C_0-C_2)$alkyl-(C_3-C_5)cycloalkyl where the alkyl and cycloalkyl groups in the definition of R^2 are optionally substituted with 1-3 fluoro groups;

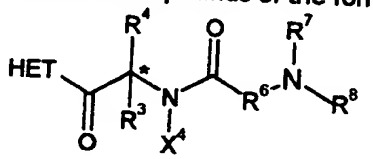
R^3 is selected form the group consisting of 3-indolyl-CH_2-, phenyl-$(CH_2)_3-$, phenyl-CH_2-O-CH_2- and thiazolyl-CH_2-O-CH_2-, where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3; and

R^{1A} is hydrogen.

A group of compounds which is preferred within the AI^A Group of compounds, designated the AI^B Group, comprises those compounds or prodrugs of such compounds or pharmaceutically acceptable salts of the compounds or prodrugs where the compound is the 3a(R,S),7a(R,S) diastereomeric mixture, the 3a(R),7a(R) diastereomer, the 3a(S),7a(S) diastereomer, the 3a(R),7a(S) diastereomer, or the 3a(S),7a(R) diastereomer of 2-amino-N-[2-(3a-benzyl-2-cyclopropyl-3-oxo-octahydro-pyrrolo[3,4-c]pyridin-5-yl)-1(R)-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide; 2-amino-N-[2-(3a-benzyl-2-methyl-3-oxo-octahydro-pyrrolo[3,4-c]pyridin-5-yl)-1(R)-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide;

or 2-amino-N-[1(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-pyridin-2-ylmethyl-octahydro-pyrrol [3,4-c]pyridin-5-yl)-2-oxo-ethyl]-2-methyl-propi namide.

This invention also provides compounds of the formula

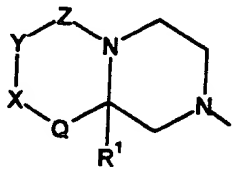


I

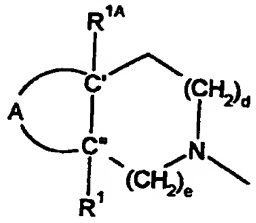
or a stereoisomeric mixture thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomer thereof, or a prodrug of such compound, mixture or isomer thereof, or a pharmaceutically acceptable salt of the compound, mixture, isomer or prodrug,

wherein

HET is a heterocyclic moiety selected from the group consisting of



and



d is 0, 1 or 2;

e is 1 or 2;

A is a divalent radical, where the left hand side of the radical as shown below is connected to C" and the right hand side of the radical as shown below is connected to C', selected from the group consisting of

-C(R^9R^{10})-NR^2-C(O)-,

-C(R^9R^{10})-C(R^9R^{10})-C(R^9R^{10})-,

-S(O)$_2$-C(R^9R^{10})-C(R^9R^{10})-,

-C(R^9R^{10})-O-C(O)-,

-C(R^9R^{10})-O-C(R^9R^{10})-,

-NR^2-C(O)-C(R^9R^{10})-,

-O-C(O)-C(R^9R^{10})-,

-C(R^9R^{10})-C(O)-NR^2-,

-C(R^9R^{10})-C(O)-O-,

-C(O)-NR^2-$C(R^9R^{10})$-$C(R^9R^{10})$-,
-C(O)-O-$C(R^9R^{10})$-,
-$C(R^9R^{10})$-$C(R^9R^{10})$-$C(R^9R^{10})$-$C(R^9R^{10})$-,
-$S(O)_z$-NR^2-$C(R^9R^{10})$-$C(R^9R^{10})$-,
-$C(R^9R^{10})$-$C(R^9R^{10})$-NR^2-C(O)-,
-$C(R^9R^{10})$-$C(R^9R^{10})$-O-C(O)-,
-NR^2-C(O)-$C(R^9R^{10})$-$C(R^9R^{10})$-,
-NR^2-$S(O)_z$-$C(R^9R^{10})$-$C(R^9R^{10})$-,
-O-C(O)-$C(R^9R^{10})$-$C(R^9R^{10})$-,
-$C(R^9R^{10})$-$C(R^9R^{10})$-C(O)-NR^2-,
-$C(R^9R^{10})$-$C(R^9R^{10})$-C(O)-,
-$C(R^9R^{10})$-NR^2-C(O)-O-,
-$C(R^9R^{10})$-O-C(O)-NR^2,
-$C(R^9R^{10})$-NR^2-C(O)-NR^2-,
-NR^2-C(O)-O-$C(R^9R^{10})$-,
-NR^2-C(O)-NR^2-$C(R^9R^{10})$-,
-NR^2-$S(O)_z$-NR^2-$C(R^9R^{10})$-,
-O-C(O)-NR^2-$C(R^9R^{10})$-,
-$C(R^9R^{10})$-NR^{12}-$C(R^9R^{10})$-,
-NR^{12}-$C(R^9R^{10})$-,
-NR^{12}-$C(R^9R^{10})$-$C(R^9R^{10})$-,
-C(O)-O-$C(R^9R^{10})$-$C(R^9R^{10})$-,
-$C(R^9R^{10})$-$C(R^9R^{10})$-$N(R^{12})$-,
-$C(R^9R^{10})$-NR^{12}-,
-$C(R^9R^{10})$-$C(R^9R^{10})$-NR^2-$S(O)_z$-,
-$C(R^9R^{10})$-$C(R^9R^{10})$-$S(O)_2$-NR^2-,
-$C(R^9R^{10})$-$C(R^9R^{10})$-C(O)-O-,
-$C(R^9R^{10})$-$S(O)_z$-$C(R^9R^{10})$-,
-$C(R^9R^{10})$-$C(R^9R^{10})$-$S(O)_z$-,
-O-$C(R^9R^{10})$-$C(R^9R^{10})$-,
-$C(R^9R^{10})$-$C(R^9R^{10})$-O-,
-$C(R^9R^{10})$-C(O)-$C(R^9R^{10})$-,
-C(O)-$C(R^9R^{10})$-$C(R^9R^{10})$- and

$-C(R^9R^{10})-NR^2-S(O)_2-NR^2-$;

Q is a covalent bond or CH_2;

W is CH or N;

X is $CR^{9a}R^{10a}$, $C=CH_2$ or C=O;

Y is CR^9R^{10}, O or NR^2;

Z is C=O, C=S or $S(O)_2$;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)S(O)_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)S(O)_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)S(O)_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro groups;

Y^1 is O, $S(O)_m$, $-C(O)NX^6-$, -CH=CH-, -C≡C-, $-N(X^6)C(O)-$, $-C(O)NX^6-$, -C(O)O-, $-OC(O)N(X^6)-$ or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group in the definition of R^1 are optionally independently substituted with hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro groups or 1 or 2 (C_1-C_4)alkyl groups;

R^{1A} is selected from the group consisting of hydrogen, F, Cl, Br, I, (C_1-C_6)alkyl, phenyl(C_1-C_3)alkyl, pyridyl(C_1-C_3)alkyl, thiazolyl(C_1-C_3)alkyl and thienyl(C_1-C_3)alkyl, provided that R^{1A} is not F, Cl, Br or I when a heteroatom is vicinal to C";

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxy, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, -

$S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^5)$, CF_3, CN or 1, 2 or 3 independently selected halo groups;

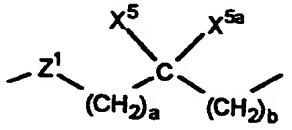
R^3 is selected from the group consisting of A^1, (C_1-C_{10})alkyl, $-(C_1-C_6)$alkyl-A^1, $-(C_1-C_6)$alkyl-(C_3-C_7)cycloalkyl, $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl, $-(C_1-C_5)$alkyl-X^1-(C_0-C_5)alkyl-A^1 and $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl-(C_3-C_7)cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 independently selected halo groups or 1, 2 or 3 independently selected $-OX^3$ groups;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_6)alkyl or (C_3-C_7)cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7)cycloalkyl, (C_5-C_7)cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6)alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are each independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, CF_3, A^1 and optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^2$, (C_3-C_7)cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen at m bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then only one of X^5 or X^{5a} is on the carbon atom and only one of R^7 or R^8 is on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or N-X^2, provided that when a and b are both 0 then Z^1 is not N-X^2 or O;

R^7 and R^8 are each independently hydrogen or optionally substituted (C_1-C_6)alkyl;

where the optionally substituted (C_1-C_6)alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, -C(O)O-(C_1-C_6)alkyl, -S(O)$_m$(C_1-C_6)alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 -O-C(O)(C_1-C_{10})alkyl groups or 1 to 3 (C_1-C_6)alkoxy groups; or

R^7 and R^8 can be taken together to form -$(CH_2)_r$-L-$(CH_2)_r$-;

where L is C(X^2)(X^2), S(O)$_m$ or N(X^2);

R^9, R^{9a}, R^{10} and R^{10a} are each independently hydrogen, fluoro, hydroxy, (C_1 - C_4)alkoxy or (C_1 - C_5)alkyl optionally substituted with 1 to 5 halogroups, provided that at least one of R^9, R^{9a}, R^{10} or R^{10a} is present and is (C_1 - C_4)alkoxy;

R^{11} is selected from the group consisting of (C_1-C_5)alkyl and phenyl optionally substituted with 1-3 substitutents each independently selected from the group consisting of (C_1-C_5)alkyl, halo and (C_1-C_5)alkoxy;

R^{12} is selected from the group consisting of (C_1-C_5)alkylsulfonyl, (C_1-C_5)alkanoyl and (C_1-C_5)alkyl where the alkyl portion is optionally independently substituted by 1-5 halo groups;

A^1 for each occurrence is independently selected from the group consisting of (C_5-C_7)cycloalkenyl, phenyl, a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen and a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, on one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-S(O)_2N(X^6)(X^6)$, $-N(X^6)S(O)_2$-phenyl, $-N(X^6)S(O)_2X^6$, $-CONX^{11}X^{12}$, $-S(O)_2NX^{11}X^{12}$, $-NX^6S(O)_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6S(O)_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 (C_1-C_{10})alkanoyloxy groups or 1 to 3 (C_1-C_6)alkoxy groups;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, the X^{12} group is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl or optionally substituted (C_3-C_7)cycloalkyl, where the optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halo groups or 1-3 OX^3 groups;

X^3 for each occurrence is independently hydrogen or (C_1-C_6)alkyl;

X^6 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, (C_2-C_6)halogenated alkyl, optionally substituted (C_3-C_7)cycloalkyl, (C_3-C_7)-halogenated cycloalkyl, where optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^6 is optionally independently mono- or di-substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, carboxylate (C_1-C_4)alkyl ester or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6)alkyl, the two (C_1-C_6)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 as a ring member;

X^7 is hydrogen or (C_1-C_6)alkyl optionally substituted with hydroxy;

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

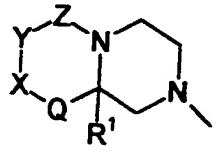
X^6 and X^{12} cannot be hydrogen when attached to C(O) or $S(O)_2$ in the form $C(O)X^6$, $C(O)X^{12}$, $S(O)_2X^6$ or $S(O)_2X^{12}$; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is independently 2 or 3.

A preferred group of compounds within the scope of the compounds disclosed in the immediately preceding paragraph, designated the ZA Group,

comprises those compounds or a stereoisomeric mixtures thereof, diastereomerically nriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers thereof, or prodrugs of such compounds, mixtures or isomers thereof, or pharmaceutically acceptable salts of the compounds, mixtures, isomers or prodrugs wherein:

HET is



R^1 is $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl or (C_1-C_{10})alkyl;

where A^1 in the definition or R^1 is phenyl, pyridyl, thiazolyl or thienyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3;

the cycloalkyl and alkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy or 1 to 3 fluoro atoms;

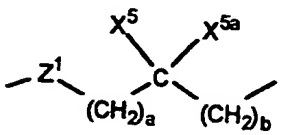
q is 1 or 2;

t is 1 or 2;

R^3 is selected form the group consisting of phenyl-CH_2-O-CH_2-, phenyl-CH_2-S-CH_2-, pyridyl-CH_2-O-CH_2-, thienyl-CH_2-O-CH_2-, 3-indolyl-CH_2-, phenyl-$(CH_2)_3$- and thiazolyl-CH_2-O-CH_2-; where the carbon atom bearing the substituent R^3 is of the (R)-configuration;

where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3

R^4 is hydrogen;

R^6 is  where Z^1 is a bond; X^5 and X^{5a} are each methyl; a and b are each 0;

R^7 and R^8 or ach hydrogen;

X^4 is hydrogen.

A group of compounds which is preferred within the ZA Group of compounds, designated the ZB Group, comprises those compounds or stereoisomeric mixtures thereof, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers thereof, or prodrugs of such compounds, mixtures or isomers thereof, or pharmaceutically acceptable salts of the compounds, mixtures, isomers or prodrugs wherein:

Z is C=O; Q is a covalent bond;

Y is CR^9R^{10}

where R^9 in the definition of Y is selected from the group consisting of hydrogen, fluoro, hydroxy, (C_1-C_2)alkoxy and (C_1-C_2)alkyl optionally substituted with 1-3 fluoro groups; and R^{10} in the definition of Y is selected from the group consisting of hydrogen, fluoro, and (C_1-C_2)alkyl optionally substituted with 1-3 fluoro groups with the proviso that R^{10} cannot be fluoro when R^9 is hydroxy or (C_1-C_2)alkoxy;

and X is CHR^{9a}

where R^9 in the definition of X is selected from the group consisting of hydrogen, fluoro, hydroxy, (C_1-C_2)alkoxy and (C_1-C_2)alkyl optionally substituted with 1-3 fluoro groups.

R^1 is $-CH_2-A^1$

where A^1 is phenyl, pyridyl or thiazolyl, optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3; and

R^3 is selected form the group consisting of 3-indolyl-CH_2-, phenyl-$(CH_2)_3$-, phenyl-CH_2-O-CH_2- and thiazolyl-CH_2-O-CH_2-,

where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, CH_3, OCH_3, OCF_2H, OCF_3 and CF_3.

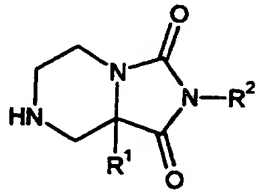
A group of compounds which is preferred within the ZB Group of compounds, designated the ZC Group, comprises those compounds or prodrugs of such compounds or pharmaceutically acceptable salts of the compounds or prodrugs wh re the compound is the 8(R,S),8a(R,S) diastere meric mixture, the

8(R),8a(R) diastereomer, the 8(S),8a(S) diastereomer, the 8(R),8a(S) diastereomer, or the 8(S),8a(R) diastereomer of 2-amino-N-[1(R)-benzyloxymethyl-2-(8-methoxy-6-oxo-8a-pyridin-2-ylmethyl-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-2-oxo-ethyl]-2-methyl-propionamide.

This invention also provides methods of treating or preventing sleep disorders in a mammal, including humans or other animals such as especially dogs, cats and horses, which comprise administereing to such human or other animal an effective amount of a compound of Formula I.

This invention also provides the L-tartrate salt of 2-amino-N-{1-(R)-benzyloxymethyl-2-[1,3-dioxo-8a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide.

This invention also provides compounds of the formula



where R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_r-A^1$, $-(CH_2)_qN(X^6)S(O)_2(CH_2)_r-A^1$, $-(CH_2)_qN(X^6)S(O)_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_r-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_r-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_r-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_r-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_r-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_r-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)S(O)_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_r-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_r-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_r-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_r-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro groups;

Y^1 is O, $S(O)_m$, $-C(O)NX^6-$, -CH=CH-, $-C\equiv C-$, $-N(X^6)C(O)-$, $-C(O)NX^6-$, -C(O)O-, $-OC(O)N(X^6)-$ or -OC(O)-;

m for each occurrence is 0, 1 or 2;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group in the definition of R^1 are optionally independently substituted with hydroxy, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro groups or 1 or 2 (C_1-C_4)alkyl groups;

A^1 for each occurrence is independently selected from the group consisting of (C_5-C_7)cycloalkenyl, phenyl, a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen and a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, on one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-S(O)_2N(X^6)(X^6)$, $-N(X^6)S(O)_2$-phenyl, $-N(X^6)S(O)_2X^6$, $-CONX^{11}X^{12}$, $-S(O)_2NX^{11}X^{12}$, $-NX^6S(O)_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6S(O)_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 (C_1-C_{10})alkanoyloxy groups or 1 to 3 (C_1-C_6)alkoxy groups;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thi nyl, provided that when X^{12} is not hydrogen, the X^{12} group is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

X^6 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, (C_2-C_6)halogenated alkyl, optionally substituted (C_3-C_7)cycloalkyl, (C_3-C_7)-halogenated cycloalkyl, where optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^6 is optionally independently mono- or di-substituted with (C_1-C_4)alkyl, hydroxy, (C_1-C_4)alkoxy, carboxyl, $CONH_2$,

$-S(O)_m(C_1-C_6)$alkyl, carboxylate (C_1-C_4)alkyl ester or 1H-tetrazol-5-yl; or when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6)alkyl, the two (C_1-C_6)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 as a ring member; and

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxy, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 independently selected halo groups.

A group of compounds which is preferred within the compounds disclosed within the immediately preceding paragraph, designated the XA Group, comprises those compounds wherein R^1 is CH_2-A^1 and R^2 is CF_3CH_2-.

A group of compounds which is preferred within the XA Group of compounds, designated the XB Group, comprises those compounds wherein A^1 is 2-pyridyl.

A compound which is pref rred within the XB Group of compounds is 8a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-tetrahydro-imidazo[1,5-a]pyrazine-1,3-dione.

Another compound which is preferred within the XB group of compounds is the L-tartrate salt of 8a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-tetrahydro-imidazo[1,5-a]pyrazine-1,3-dione.

This invention also provides a process for preparing 1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazine-7-carboxylic acid tert-butyl ester comprising reacting 8a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-tetrahydro-imidazo[1,5-a]pyrazine-1,3-dione with D-tartaric acid in a reaction inert solvent at 0°C to about room temperature for about 5 minutes to about 48 hours.

This invention also provides a process for preparing 2-amino-N-(1(R)-benzyloxymethyl-2-(1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-methyl-propionamide hydrochloride comprising

(a) reacting 8a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-tetrahydro-imidazo[1,5-a]pyrazine-1,3-dione with D-tartaric acid in a reaction inert solvent to form 1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazine-7-carboxylic acid tert-butyl ester;

(b) reacting said 1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazine-7-carboxylic acid tert-butyl ester with 3-benzyloxy-2-(2-tert-butoxycarbonylamino-2-methyl-propionylamino)-propionic acid in the presence of a tertiary amine and 1-propanephosphonic acid cyclic anhydride in a reaction inert solvent to form (1-(1(R)-benzyloxymethyl-2-(1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester; and

(c) reacting said (1-(1(R)-benzyloxymethyl-2-(1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-oxo-ethylcarbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester with concentrated hydrochloric acid in a reaction inert solvent to form 2-amino-N-(1(R)-benzyloxymethyl-2-(1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl)-2-m thyl-propionamide hydrochloride.

Detailed Description of the Invention

In general the compounds of Formula I can be made by processes known in the chemical arts. Certain processes for the manufacture of Formula I compounds are provided as further features of the invention and are illustrated by the following reaction schemes.

In the above structural formulae and throughout the instant application, the following terms have the indicated meanings unless expressly stated otherwise:

The alkyl groups are intended to include those alkyl groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, ethynyl, propenyl, butadienyl, hexenyl and the like.

When the definition C_0-alkyl occurs in the definition, it means a single covalent bond.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy, allyloxy, 2-propynyloxy, isobutenyloxy, hexenyloxy and the like.

The term "halogen" or "halo" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

The term "halogenated alkyl" is intended to include an alkyl group as defined hereinabove substituted by one or more halogen atoms as defined hereinabove.

The term "halogenated cycloalkyl" is intended to include a cycloalkyl group substituted by one or more halogen atoms as defined hereinabove.

The term "aryl" is intended to include phenyl and naphthyl and aromatic 5- and 6-membered rings with 1 to 4 heteroatoms or fused 5- and/or 6-membered bicyclic rings with 1 to 4 heteroatoms of nitrogen, sulfur or oxygen. Examples of such heterocyclic aromatic rings are pyridine, thiophene (also known as thienyl), furan, benzothiophene, tetrazole, indole, N-methylindole, dihydroindole, indazole, N-formylindole, benzimidazole, thiazole, pyrimidine, and thiadiazole.

Th expression "prodrug" refers to compounds that are drug precursors which following administration, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH is converted to the desired drug form). Exemplary prodrugs upon cleavage release the corresponding free acid, and such hydrolyzable ester-forming residues of the compounds of this invention include but are not limited to carboxylic acid substituents (e.g., when R^1 is $-(CH_2)_qC(O)OX^6$ where X^6 is hydrogen, or when R^2 or A^1 contains carboxylic acid) wherein the free hydrogen is replaced by (C_1-C_4)alkyl, (C_2-C_{12})alkanoyloxymethyl, (C_4-C_9)1-(alkanoyloxy)ethyl, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)-alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl.

Other exemplary prodrugs release an alcohol of Formula I wherein the free hydrogen of the hydroxyl substituent (e.g., when R^1 contains hydroxyl) is replaced by (C_1-C_6)alkanoyloxymethyl, 1-$((C_1-C_6)$alkanoyloxy)ethyl, 1-methyl-1-$((C_1-C_6)$alka-noyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxy-carbonylamino-methyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacetyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl wherein said α-aminoacyl moieties are independently any of the naturally occurring L-amino acids found in proteins,

$-P(O)(OH)_2$, $-P(O)(O(C_1-C_6)alkyl)_2$ or glycosyl (the radical resulting from detachment of the hydroxyl of the hemiacetal of a carbohydrate).

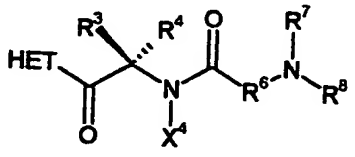
Prodrugs of this invention where a carboxyl group in a carboxylic acid of Formula I is replaced by an ester may be prepared by combining the carboxylic acid with the appropriate alkyl halide in the presence of a base such as potassium carbonate in an inert solvent such as DMF at a temperature of about 0°C to 100°C for about 1 to about 24 hours. Alternatively, the acid is combined with the appropriate alcohol as solvent in the presence of a catalytic amount of acid such as

concentrated sulfuric acid at a temperature f about 20°C to 120°C, pref rably at reflux, for ab ut 1 hour to about 24 hours. Another method is the reaction of the acid in an inert solvent such as THF, with concomitant removal of the water being produced by physical (e.g., Dean Stark trap) or chemical (e.g., molecular sieves) means.

Prodrugs of this invention where an alcohol function has been derivatized as an ether may be prepared by combining the alcohol with the appropriate alkyl bromide or iodide in the presence of a base such as potassium carbonate in an inert solvent such as DMF at a temperature of about 0°C to 100°C for about 1 to about 24 hours. Alkanoylaminomethyl ethers may be obtained by reaction of the alcohol with a bis-(alkanoylamino)methane in the presence of a catalytic amount of acid in an inert solvent such as THF, according to a method described in US 4,997,984. Alternatively, these compounds may be prepared by the methods described by Hoffman et al. in J. Org. Chem. 1994, 59, p. 3530.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in the structural Formula I. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers, racemic mixtures or diastereomeric mixtures thereof, be included within the scope of the instant invention. In the case of the asymmetric center represented by the asterisk, it has been found that the absolute stereochemistry of the more active and thus more preferred isomer is shown in Formula IA. This preferred absolute configuration also applies to Formula I.



IA

With the R^4 substituent as hydrogen, the spatial configuration of the asymmetric center corresponds to that in a D-amino acid. In most cases this is also designated an R-configuration although this will vary according to the values of R^3 and R^4 used in making R- or S-stereochemical assignments.

The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, D-tartaric, L-tartaric, malonic, methane sulfonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counter-ion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

The pharmaceutically acceptable salts are formed by taking about 1 equivalent of a compound of Formula I and contacting it with about 1 equivalent of the appropriate corresponding acid of the salt which is desired. Work-up and isolation of the resulting salt is well-known to those of ordinary skill in the art.

The growth hormone releasing compounds of Formula I are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release.

The compounds of Formula I can be administered to animals, including humans, to release growth hormone *in vivo*. The compounds are useful for treating symptoms related to GH deficiency; stimulating pre- and post-natal growth or enhancing feed efficiency and improving carcass quality of animals raised for meat production; increasing milk production in dairy cattle; improving estrous synchronization in livestock such as swine, beef and dairy cattle; improving bone or wound healing and improving vital organ function in animals. The compounds of the present invention, by inducing endogenous GH secretion, will alter body composition and modify other GH-dependent metabolic, immunologic or

dev lopmental processes. For example, the compounds of the pres nt invention can be giv n t chickens, turkeys, livestock animals (such as sheep, pigs, horses, cattle, etc.) and companion animals (e.g., dogs). These compounds may also have utility in aquaculture to accelerate growth and improve the percent lean meat. In addition, these compounds can be administered to humans *in vivo* as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I or a pharmaceutically acceptable salt or prodrug thereof can be administered *in vivo* to children and serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I or a pharmaceutically acceptable salt or prodrug thereof in association with a pharmaceutically acceptable carrier. Optionally, the pharmaceutical compositions can further comprise an anabolic agent in addition to at least one of the compounds of Formula I or a pharmaceutically acceptable salt or prodrug thereof, or another compound which exhibits a different activity, e.g., an antibiotic or coccidiostat (e.g., monensin) growth promotant or an agent to treat osteoporosis or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

Growth promoting and anabolic agents include, but are not limited to, TRH, PTH, diethylstilbesterol, estrogens, ß-agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, the disclosure of which is hereby incorporated by reference, e.g., zeranol; compounds disclosed in U.S. Patent No. 4,036,979, the disclosure of which is hereby incorporated by reference, e.g., sulbenox; and peptides disclosed in U.S. Patent No. 4,411,890, the disclosure of which is hereby incorporated by reference.

The growth hormone secretagogues of this invention in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6 and GHRP-1 as described in U.S. Patent No. 4,411,890, the disclosure of which is hereby incorporated by reference, and publications WO

89/07110, WO 89/07111 and B-HT920 as well as hexarelin and the newly discovered GHRP-2 as described in WO 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 or alpha-2-adrenergic agonists such as clonidine, xylazine, detomidine and medetomidine or serotonin 5HTID agonists such as sumitriptan or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine, are useful for increasing the endogenous levels of GH in mammals. The combination of a GH secretagogue of this invention with GRF results in synergistic increases of endogenous growth hormone.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous [See "Human Growth Hormone", Strobel and Thomas, Pharmacological Reviews, 46, pg. 1-34 (1994); T. Rosen et al., Horm Res, 1995; 43: pp. 93-99; M. Degerblad et al., European Journal of Endocrinology, 1995, 133: pp.180-188; J. O. Jorgensen, European Journal of Endocrinology, 1994, 130: pp. 224-228; K. C. Copeland et al., Journal of Clinical Endocrinology and Metabolism, Vol. 78 No. 5, pp. 1040-1047; J. A. Aloi et al., Journal of Clinical Endocrinology and Metabolism, Vol. 79 No. 4, pp. 943-949; F. Cordido et al., Metab. Clin. Exp., (1995), 44(6), pp. 745-748; K. M. Fairhall et al., J. Endocrinol., (1995), 145(3), pp. 417-426; R.M. Frieboes et al., Neuroendocrinology, (1995), 61(5), pp. 584-589; and M. Llovera et al., Int. J. Cancer, (1995), 61(1), pp. 138-141]. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses of growth hormone may be summarized as follows: stimulating growth hormone release in elderly humans or companion animals especially dogs, cats, camels and horses; treating growth hormone deficient adult humans or other animals especially dogs, cats, camels and horses; preventing catabolic side effects of glucocorticoids, treating osteoporosis, stimulating the immune system, accelerating wound healing, accelerating bone fracture repair, treating growth retardation, treating congestive heart failure as disclosed in PCT publications WO 95/28173 and WO 95/28174 (an example of a method for assaying growth hormone secretagogues for efficacy in treating congestive heart failure is disclosed in R. Yang et al., Circulation, Vol. 92, No. 2, p.262, 1995), treating acute r chronic renal failure or insufficiency; treating

physi l gical short stature including growth horm n deficient children, treating short stature associated with chronic illness, treating obesity, treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treating intrauterine growth retardation, skeletal dysplasia, hypercortisonism and Cushings syndrome; replacing growth hormone in stressed patients; treating osteochondrodysplasias, Noonans syndrome, sleep disorders, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treating pulmonary dysfunction and ventilator dependency; attenuating protein catabolic response after a major operation; treating malabsorption syndromes, reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treating hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; stimulating thymic development and preventing age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treating immunosuppressed patients and enhancing antibody response following vaccination; improving muscle strength, increasing muscle mass, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulating osteoblasts, bone remodeling, and cartilage growth; treating neurological diseases such as peripheral and drug induced neuropathy, Guillian-Barre Syndrome, amyotrophic lateral sclerosis, multiple sclerosis, cerebrovascular accidents and demyelinating diseases; and stimulating wool growth in sheep.

Uses of GH in farm animals raised for meat production such as chickens, turkeys, sheep, pigs and cattle include stimulation of pre- and post- natal growth, enhanced feed efficiency in animals raised for meat production, improved carcass quality (increased muscle to fat ratio) (Campbell, R. G. et al., (1989), J. Anim. Sci. 67, 1265; Dave, D. J., Bane, D. P., (1990), The Compendium Food Anual, Vol. 12(1), 117; Holden, P. J., (1990), Agri-Practice, 11(3), 25; Claus, R., Weiber, U., (1994), Livestock Production Science, 37, 245; Roeder, R. et al., (1994), Growth Regulation, 4, 101); increased milk production in dairy cattle (McBride, B. W. et al., (1988), Research and Development in Agriculture 5(1), 1; McDowell, G. H. et al.,

(1988), Aust. J. Biol. Sci., 41, 279); improved body composition; modification of oth r GH-dependent metabolic (Claus, R. and Weiber, U., (1994), Livestock Production Science, 37, 245) and immunologic functions such as enhancing antibody response following vaccination or improved developmental processes; and may have utility in aquaculture to accelerate growth and improve the protein-to-fat ratio in fish.

Preferred uses in companion animals include stimulating endogenous growth hormone release in companion animals such as dogs, cats and horses; treating disorders of aging (Detenbeck, L. C., Jowsey, J., Clinical Orthopedics and Related Research, July-August 1969, No. 65, pp. 76-80); stimulating thymic development and preventing age-related decline of thymic function (Goff, B. L. et al., Clinical and Experimental Immunology, 1987, 68:3, pp. 580-587; Morrison, W. B. et al., Am. J. Vet. Res., Jan. 1990, 51:1, pp. 65-70; Roth, J. A. et al., Am. J. Vet. Res., 1984, Vol. 45, pp. 1151-1155); preventing age-related decline of thymic function; preventing age-related decline in cognition; accelerating wound healing (Jacks, T. et al., Vet. Surg. 1996, 25, (5), 430); accelerating bone fracture repair (Pandey, S. K., Udupa, K. N., Indian J. Vet. Surg. 1 (2): 73-78, July 1980); stimulating osteoblasts, bone remodelling and cartilage growth (Harris, W. H. et al., Calc. Tiss. Res., 10, 1972, pp. 1-13; Heaney, R. P. et al., Calc. Tiss. Res. 10, 1972, pp. 14-22; Mankin. H. J. et al., J. of Bone and Joint Surgery, Vol. 60-A, #8, Dec. 1978, pp. 1071-1075); attenuating protein catabolic response after major surgery, accelerating recovery from burn injuries and major surgeries such as gastrointestinal surgery; stimulating the immune system and enhancing antibody response following vaccination; treating congestive heart failure, treating acute or chronic renal failure or insufficiency, treating obesity; treating growth retardation, skeletal dysplasia and osteochondrodysplasias; preventing catabolic side effects of glucocorticoids; treating Cushing's syndrome; treating malabsorption syndromes, reducing cachexia and protein loss due to chronic illness such as cancer; accelerating weight gain and protein accretion in animals receiving total parenteral nutrition; providing adjuvant treatment for ovulation induction and to prevent gastrointestinal ulcers; improving muscle mass, strength and mobility; maintenance of skin thickness, and improving vital organ function and metabolic homeostasis.

The growth hormone secretagogues of this invention, compounds of Formula I, or a pharmaceutically acceptable salt or prodrug thereof in combination with an alpha-2 adrenergic agonist are useful in promoting GH secretion in humans and other animals (See Cella, S. G. et al., Acta Endocrinologica (Copenh.) 1989, 121, pp. 177-184). As such, a combination of a compound of Formula I or a pharmaceutically acceptable salt or prodrug thereof and an alpha-2 adrenergic agonist is useful in the treatment or prevention of frailty associated with aging, congestive heart failure and obesity which comprises administering to a human or another animal, especially dogs, cats and horses, in need of such treatment a combination of an alpha-2 adrenergic agonist and a compound of Formula I or a pharmaceutically acceptable salt or prodrug thereof, defined above. Preferred alpha-2 adrenergic agonists include clonidine, which is disclosed in US Patent No. 3,202,660 the disclosure of which is hereby incorporated by reference, xylazine, which is disclosed in US Patent No. 3,235,550 the disclosure of which is hereby incorporated by reference and medetomidine, which is disclosed in US Patent No. 4,544,664 the disclosure of which is hereby incorporated by reference. In another aspect, this invention provides methods for accelerating bone fracture repair and wound healing, attenuating protein catabolic response after a major operation, and reducing cachexia and protein loss due to chronic illness, which comprise administering to a human or another animal, especially dogs, cats and horses in need of such treatment a combination of an alpha-2 adrenergic agonist such as clonidine, xylazine or medetomidine and a compound of Formula I or a pharmaceutically acceptable salt or prodrug thereof. It has been shown that alpha-2 adrenergic agonists cause release of endogenous growth hormone in human and canine subjects (Cella et al., Life Sciences (1984), 34:447-454; Hampshire J, Altszuler N., American Journal of Veterinary Research (1981), 42:6, 1073-1076; Valcavi et al., Clinical Endocrinology (1988), 29:309-316; Morrison et al., American Journal of Veterinary Research (1990), 51:1, 65-70;), and that the co-administration of an alpha-2 adrenergic agonist with growth hormone-releasing factor restores defective growth hormone secretion in aged dogs (Arce et al., Brain Research (1990), 537:359-362; Cella et. al., Neuroendocrinology (1993), 57:432-438).

This invention also relates to a method of treating insulin resistant conditions such as Non-Insulin Dependent Diabetes Mellitus (NIDDM) and reduced glycemic